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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,248	09/19/2003	Lindsay Schwarz	D5806D	5577

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,248	SCHWARZ ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the papers filed November 21, 2005. Applicant's response to restriction requirement of October 19, 2005 has been entered. The paper amended claim 2. No claims were canceled or withdrawn. Currently, claims 1-17 are pending in the application.

Election/Restrictions

Applicant's election of species, drawn to beclomethasone, lung, injection, administration of glucocorticoid prior to delivery of the gene, non-human animals, synthetic glucocorticoid, cationic lipid transfection, recombinant genes and plasmid, is acknowledged. In addition to beclomethasone, the glucocorticoid species of dexamethasone has been included in the examination of the instant application. The election was made without traverse; the restriction requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 and 14-17 are rejected under 35 USC 103(a) as being unpatentable over Malone et al. (J. Biol. Chem. 269(47):29903-29907, 1994), in view of Debs (US Pat No. 5,756,353; filed Jun. 7, 1995), as evidenced by the as filed specification, stating that the promoters used in the claimed invention (that include CMV) do not have a common GRE, as determined by searching the gene bank sequences (page 40, lines 11-13).

Claims 1-12 and 14-17 embrace a method of increasing the cellular expression of a gene in a biological tissue in an animal for gene therapy, comprising delivering said gene, under the control of a

promoter that does not have a glucocorticoid response element (GRE), to said animal and additionally administering a pharmacologically effective dose of a glucocorticoid.

Malone et al. describe the direct injection of plasmid DNA containing a gene under the control of the CMV promoter into the livers of rats and cats (non-human animals). They further describe that treatment with the glucocorticoid dexamethasone enhanced and prolonged transfected gene expression (Abstract).

Regarding the claim 3 dose limitation range of glucocorticoid administered, Malone et al. state: "Dexamethasone treatment of rats consisted of daily subcutaneous injections of 1 mg/kg" (under Experimental Procedures, p. 29903), that is within the range stated in claim 3.

In reference to the limitations of solvent and delivery via injections (claims 7 and 8), Malone et al. state: "500 μg of plasmid DNA (dilute in 2-3 ml of Dulbecco's modified Eagle medium), was injected directly into the hepatic parenchyma". Further stating: " Cats were treated with daily subcutaneous injections of 0.3 mg/kg dexamethasone, with a 1 mg/kg pre-treatment dose the day prior to plasmid injection" (under Experimental Procedures, p. 29903).

It should be noted that the glucocorticoid described by Malone et al. is dexamethasone and not the elected species of claim 2, beclomethasone. In view of the inclusion of dexamethasone as a glucocorticoid species cited in claim 2 and MPEP 2144.07, under art recognized suitability for an intended purpose, "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In the instant case, both beclomethasone and dexamethasone represent synthetic glucocorticoids that enhance the expression of genes under the control of the CMV promoter.

While Malone et al. do not specifically describe the use of glucocorticoids for applications involving gene therapy, wherein the increased expression of a gene of interest enhances treatment of a pathophysiological state in an animal, Malone et al. state: "Enhancement of transfected gene expression *in vivo* after treatment with dexamethasone demonstrates that pharmacologically defined polynucleotide delivery systems will be useful for analyses of the *in vivo* interactions of genes and organisms" (last paragraph, first column, p. 29907). Further, on page 29903, second column, first paragraph, they state: "Acute hepatic inflammation likely occurred at the site of direct injection and possibly reduced expression from transfected genes. To overcome this possible inflammation, animals

were treated with dexamethasone, resulting in enhanced and prolonged gene expression", thus providing the motivation to apply treatment with glucocorticoids to enhance gene expression in settings where the enhanced expression of a gene is desired to treat a pathophysiological state.

Debs et al. describe liposome-nucleic acid complexes that are delivered to the lung, with subsequent *in vivo* expression of a protein encoded by the delivered gene, for gene therapy in a mammalian subject (Abstract and column 2, third paragraph). In column 2, fourth paragraph, Debs et al. state: "the nucleic acid used is DNA and the liposome is a cationic liposome". Column 6, third paragraph states: "The present invention is particularly useful for the delivery of substances directly into the lung for the prevention and/or treatment of pulmonary disorders such as lung cancer, emphysema, asthma, lung infections such as chronic bronchitis and pneumonia, degenerative diseases of the lung, as well as genetic disorders such as cystic fibrosis and α-1 antitrypsin deficiency". Column 14, fifth paragraph states: "Also tested was a plasmid containing the CAT gene driven by the CMV promoter" (thus representing a recombinant gene). Additional promoters are also described, including SV40 (column 8, fifth paragraph) and column 9, first paragraph states: "Other types of regulatory elements may also be present in the vector, for example, enhancer sequences".

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of glucocorticoid inducible promoters such as CMV operably linked to a therapeutic gene for delivery to an animal, together with a pharmacologically effective dose of a glucocorticoid, in an amount sufficient to increase the expression of said gene, to enhance the treatment of the pathophysiological state of said animal, resulting in the practice of the instantly claimed invention. The state of the art at the time of the invention had demonstrated the routine methods for expression of genes under the control of promoters such as CMV and *in vivo* transfection of said genes for gene therapy. Therefore, an artisan of skill, having combined the elements of a non-GRE promoter and a therapeutic gene, a delivery means for transfer of said gene to an animal and concurrent, prior or post gene delivery treatment with a glucocorticoid, would have a reasonable expectation of success in sufficiently increasing the cellular expression of said gene in the biological tissue of said animal to enhance treatment of a pathophysiological state of the animal. Claims 2-16 depend from claim 1.

Claim 13 is rejected under 35 USC 103(a) as being unpatentable over Malone et al. (J. Biol. Chem. 269(47):29903-29907, 1994), in view of Debs (US Pat No. 5,756,353; filed Jun. 7, 1995), as applied to claims 1-12 and 14-17 above, and further in view of Zhou et al. (Biochimica et Biophys. Acta 1189:195-203, 2004).

While neither Malone or Debs describe a method of cationic lipid transfection, wherein the cationic amine is poly-L-lysine, at the time of the invention by Applicant, Zhou et al. describe DNA transfection mediated by cationic liposomes containing lipopoly L-Lysine and a helper lipid (Abstract). Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of glucocorticoid inducible promoters such as CMV operably linked to a therapeutic gene for cationic lipopoly L-lysine mediated delivery to an animal, together with a pharmacologically effective dose of a glucocorticoid, in an amount sufficient to increase the expression of said gene, to enhance the treatment of the pathophysiological state of said animal, resulting in the practice of the instantly claimed invention. Therefore, an artisan of skill, having combined the elements of a non-GRE promoter and a therapeutic gene, a delivery means for transfer of said gene to an animal and concurrent, prior or post gene delivery treatment with a glucocorticoid, would have a reasonable expectation of success in sufficiently increasing the cellular expression of said gene in the biological tissue of said animal to enhance treatment of a pathophysiological state of the animal.

Thus the claimed invention, as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claims 1-17, not allowable over the art.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633